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Cryopyrin Associated Periodic Syndromes (CAPS) (CINCA/Muckle Wells/FCAS)

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1. WHAT IS CAPS

1.1 What is it?

Cryopyrin-Associated Periodic Syndromes (CAPS) comprise a group of rare autoinflammatory diseases that include Familial Cold Autoinflammatory Syndrome (FCAS), Muckle–Wells Syndrome (MWS) and Chronic Infantile Neurologic Cutaneous Articular syndrome (CINCA), also known as Neonatal Onset Multi-systemic Inflammatory Disease (NOMID). These syndromes were initially described as distinct clinical entities despite some clinical similarities: patients often present overlapping symptoms including fever, skin eruption appearing like hives (pseudo-urticarial) and joint involvement of varying severity associated with systemic inflammation.
These three diseases exist on a continuum of severity: FCAS is the mildest condition, CINCA (NOMID) the most severe and patients with MWS have an intermediate phenotype.
Characterisations of these conditions at the molecular level have demonstrated mutations of the same gene in all three disorders.

1.2 How common is it?

CAPS are very rare conditions affecting only a few individuals per million but they are probably under-recognized. CAPS can be found worldwide.

1.3 What are the causes of the disease?

CAPS are genetic diseases. The responsible gene for the 3 clinical entities (FCAS, MWS, CINCA/NOMID) is called NLRP3 (previously referred to as CIAS1), and encodes for a protein called cryopyrin. This protein plays a key role in the inflammatory response of the body. If the gene is disrupted, it confers an increased function to the protein (called gain of function) and inflammatory responses are enhanced. These enhanced inflammatory responses are responsible for the clinical symptoms observed in CAPS.

In 30% of patients with CINCA/NOMID, no mutation of CIAS1 is found. Some "mutation negative" CAPS patients may actually have the NLRP3 mutation, but affecting too low a percentage of cells to be detected by conventional genetic tests, but still enough to cause the disease. There is some degree of genotype/phenotype correlation; mutations found in patients with mild forms of CAPS have not been identified in severely affected patients and vice versa. Additional genetic or environmental factors might also modulate severity and symptoms of disease.

1.4 Is it inherited?

CAPS are inherited as an autosomal dominant disease. This means the disease is transmitted by one of the parents who has the disease and carries an abnormal copy of CIAS1 gene. As everyone has 2 copies of all our genes, the risk of an affected parent transmitting the mutated copy of the gene CIAS1 and hence giving the disease to each child is 50%. De novo (new) mutations may also occur; in such cases, neither parent has the disease and neither carries a mutation in the NLRP3 gene but disruption of the NLRP3 gene appears upon conception. In this case, the risk of another child developing CAPS is extremely low.

1.5 Is it infectious?

CAPS are not infectious.

1.6 What are the main symptoms?

The rash — a key symptom in all three diseases — is usually the first notable symptom. Regardless of the syndrome, it exhibits the same characteristics: it is a migratory maculo-papular rash (appearing like

urticaria), usually not itching. The intensity of the skin rash can vary from patient to patient and with disease activity.
FCAS, formerly known as familial cold urticaria, is characterised by recurrent short episodes of fever, rash and joint pain precipitated by exposure to cold temperatures. Other commonly reported symptoms include conjunctivitis and muscle pain. Symptoms usually begin 1–2 hours after generalized exposure to cold temperatures or to significant variation in temperature, and the length of the attacks is usually short (less than 24 hours). These attacks are self-limiting (meaning that they resolve without treatment). Patients frequently report a pattern of feeling well in the morning after a warm night but getting worse later in the day after a cold trigger. Early onset of the disease, at birth or within the first 6 months of life, is common. Inflammation in the blood is observed during episodes of inflammation. Quality of life of patients with FCAS may be variably affected due to frequency and intensity of symptoms. However, late complications such as deafness and amyloidosis usually do not occur.

MWS is characterised by recurrent episodes of fever and rash associated with joint and eye inflammation, although fever is not always present. Chronic fatigue is very frequent.
Precipitating factors are usually not identified and cold triggering is rarely observed. The course of the disease varies between individuals from more typical recurrent attacks of inflammation to more permanent symptoms. As in FCAS, patients with MWS often describe a pattern of worsening symptoms in the evening. The first symptoms occur early in life but late presentation in childhood has been described.
Deafness is common (occurring in approximately 70% of cases) and usually begins in childhood or early adulthood; amyloidosis is the most serious complication of MWS and develops in adulthood in approximately 25% of cases. This complication is due to deposition of amyloid, a special protein related to inflammation, in some organs (such as the kidneys, gut, skin or heart). These depositions cause gradual loss of function of the organ, especially of the kidneys; it manifests as proteinuria (loss of protein in the urine) followed by impaired renal function. Amyloidosis is not specific to CAPS and it may complicate other chronic inflammatory diseases.
Inflammation in the blood is observed during episodes of inflammation or more permanently in more severe cases. Quality of life of these

patients is variably affected.

CINCA (NOMID) is associated with the most severe symptoms in this spectrum of diseases. The rash is usually the first sign and occurs at birth or in early infancy. One-third of patients may be premature or small for gestational age. Fever can be intermittent, very mild or in some cases absent. Patients frequently complain of fatigue.
Bone and joint inflammation vary in severity; in approximately two-thirds of patients, joint manifestations are limited to joint pain or transient swelling during flare-ups. In one-third of cases, however, severe and disabling joint involvement occurs as a result of cartilage overgrowth. These overgrowth arthropathies can cause gross deformity of the joints, with pain and limited range of motion. Knees, ankles, wrists and elbows are the joints most commonly affected in a symmetric pattern. Radiological manifestations are distinctive. Overgrowth arthropathies, when present, usually occur early in life, before the age of 3 years.
Abnormalities of the central nervous system (CNS) are present in almost all patients and are caused by chronic aseptic meningitis (non-infectious inflammation of the membrane surrounding the brain and spinal cord). This chronic inflammation is responsible for chronic increased intracranial pressure. Symptoms related to this condition will vary in intensity and include chronic headaches, sometimes vomiting, irritability in young children and papilloedema in fundoscopy (a specialised ophthalmologic exam). Epilepsy (seizures) and cognitive impairment occur occasionally in severely affected patients.
Eyes can also be affected by the disease; inflammation can occur at the anterior and/or posterior part of the eye, regardless the presence of papilloedema. Ocular manifestations can progress to ocular disability in adulthood (loss of vision). Perceptive deafness is frequent and develops in late childhood or later in life. Amyloidosis develops with increasing age in 25% of patients. Growth retardation and delay in the development of pubertal traits may be observed as a consequence of chronic inflammation. Blood inflammation is persistent in most cases.
Careful examination of patients with CAPS usually reveals extensive overlap of clinical symptoms. Patients with MWS might report symptoms consistent with FCAS, such as cold susceptibility (i.e. more frequent attacks in winter), or symptoms consistent with mild CNS involvement, such as frequent headaches or asymptomatic

papilloedema, as seen in patients with CINCA (NOMID). Similarly, symptoms related to neurological involvement can become obvious in patients with increasing age. Members of the same family who are affected by CAPS can present mild variability of severity; however, severe manifestations of CINCA (NOMID), such as overgrowth arthropathy or severe neurological involvement, have never been reported in members of families affected by mild forms of CAPS (FCAS or mild MWS).

1.7 Is the disease the same in every child?

Huge variability of severity is observed among CAPS. Patients with FCAS have a mild disease with good long-term prognosis. MWS patients are more severely affected, due to possible deafness and amyloidosis. CINCA/NOMID patients have the most severe disease. Among this group, variability also exists depending on the severity of neurological and joint involvement.

2. DIAGNOSIS AND THERAPY

2.1 How is it diagnosed?

Diagnosis of CAPS is based on clinical symptoms before being genetically confirmed. Distinction between FCAS and MWS or MWS and CINCA/NOMID might be difficult because of overlapping symptoms. Diagnosis is based on clinical symptoms and medical history of the patient. Ophthalmologic evaluation (in particular fundoscopy), CSF examination (lumbar puncture) and radiological evaluation are helpful in distinguishing contiguous diseases.

2.2 Can it be treated or cured?

CAPS cannot be cured since they are genetic diseases. However, thanks to substantial advances in the understanding of these disorders, new promising drugs are now available to treat CAPS and are under investigation for their long-term effect.

2.3 What are the treatments?

Recent work on the genetics and physiopathology of CAPS shows that IL-1β, a powerful cytokine (protein) of inflammation, is overproduced in these conditions and plays a major role in the onset of the disease. Currently, a number of drugs that inhibit IL-1β (IL-1 blockers) are in various stages of development. The first drug used in treating these conditions was anakinra. It was shown to be rapidly efficient in controlling inflammation, rash, fever, pain and fatigue in all CAPS. This treatment also effectively improves neurological involvement. In some conditions, it may improve deafness and control amyloidosis. Unfortunately, this drug does not seem to be effective on overgrowth arthropathy. Doses required depend on disease severity. Treatment must be started early in life, before chronic inflammation causes irreversible organ damage such as deafness or amyloidosis. It requires daily subcutaneous injection. Local reactions at the injection site are frequently reported but may resolve with time. Rilonacept is another anti-IL-1 drug approved by the FDA (Food and Drug Administration in USA) for patients older than 11 years who suffer from FCAS or MWS. Weekly subcutaneous injections are required. Canakinumab is another anti-IL-1 drug recently approved by the FDA and European Medicines Agency (EMA) for CAPS patients older than 2 years. In MWS patients, this drug has been recently shown to effectively control the inflammatory manifestations with a subcutaneous injection every 4 to 8 weeks. Due to the genetic nature of the disease, it is conceivable that the pharmacological blockade of IL-1 should be maintained for long periods, if not life-long.

2.4 How long will the disease last?

CAPS are life-long disorders.

2.5 What is the long-term prognosis (predicted outcome and course) of the disease?

The long-term prognosis of FCAS is good but quality of life can be affected by recurrent episodes of fever. In MWS syndrome, the long-term prognosis may be affected by amyloidosis and impaired renal function. Deafness is also a significant long-term complication. Children with CINCA may have growth disturbances during the course of the disease. In CINCA/NOMID, the long-term prognosis depends on the

severity of neurological, neurosensorial and joint involvements. Hypertrophic arthropathies may impose severe disabilities. Premature death is possible in severely affected patients. Treatment with IL-1 blockers has greatly improved the outcome of CAPS.

3. EVERYDAY LIFE

3.1 How might the disease affect the child and the family's daily life?

Quality of life can be affected by recurrent episodes of fever. There can often be considerable delay before the correct diagnosis is made, which may give rise to parental anxiety and sometimes to unnecessary medical procedures.

3.2 What about school?

It is essential to continue education in children with chronic diseases. There are a few factors that may cause problems for school attendance and it is therefore important to explain the child's possible needs to teachers. Parents and teachers should do whatever they can to allow the child to participate in school activities in a normal way, in order not only for the child to be successful academically but also to be accepted and appreciated by both peers and adults. Future integration in the professional world is essential for the young patient and is one of the aims of the global care of chronically ill patients.

3.3 What about sports?

Playing sports is an essential aspect of the everyday life of any child. One of the aims of therapy is to allow children to conduct a normal life as much as possible and to consider themselves not different from their peers. All activities can therefore be performed as tolerated. However, restricted physical activity or rest may be necessary during the acute phase.

3.4 What about diet?

There is no specific dietary advice. In general, the child should observe

a balanced, normal diet for his/her age. A healthy, well-balanced diet with sufficient protein, calcium and vitamins is recommended for a growing child.

3.5 Can climate influence the course of the disease?

Cold temperatures may trigger symptoms.

3.6 Can the child be vaccinated?

Yes, the child can be and should be vaccinated; however, the treating physician should be informed before administering live attenuated vaccines so that proper advice can be provided on a case-by-case basis.

3.7 What about sexual life, pregnancy, birth control?

So far, no information on this aspect in patients is available in the literature. As a general rule, like with other autoinflammatory diseases, it is better to plan a pregnancy in order to adapt treatment in advance due to the possible side effect of biologics agents on the foetus.